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Convergent preparation of 1,6-linked *C*-disaccharides via olefin metathesis

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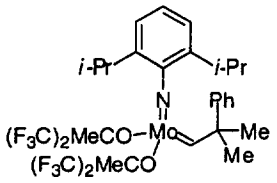
Abstract

The DCC mediated coupling reaction of 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-arabino-hex-1-enitol (**5a**) with a variety of sugar based carboxylic acids **6a–d** gave esters **7a–d** in good yield. Methylenation of the formed esters led to the acyclic enol ethers **8a–d** and exposure to the Schrock molybdenum catalyst **1** in warm toluene, in the box, gave the target *C*-disaccharide glycals **9a–d** in good yield. The 1,6-linked *gluco* based *C*-disaccharide glycal **9a** was converted to the 2-deoxy-β-*gluco*-derivative **10a** and the corresponding and *gluco* β-*gluco*-*C*-disaccharide **13**.

Keywords: glycal; metathesis; ester; *C*-disaccharide.

Olefin metathesis has attracted much attention from synthetic chemists in recent years due to the availability of several efficient metathesis pre-catalysts such as **1–4**, (Fig. 1).[1–4] Metathesis chemistry has been applied to many synthetic problems,[5] and has recently begun to find utility in the area of carbohydrate chemistry.[6]

We recently reported[7] a metathesis-based approach to the preparation of a variety of *C*-glycosides, compounds in which the glycosidic oxygen atom has been replaced by a carbon atom. These are biologically relevant compounds with potential as enzyme inhibitors and stable sugar mimics.[8] In this



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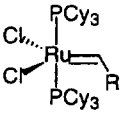
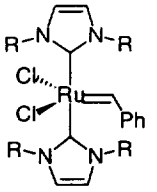


2a: R = CH=CPh$_2$
2b: R = Ph



3a: R = *i*Pr
3b: R = Cy

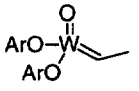


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Figure 1.

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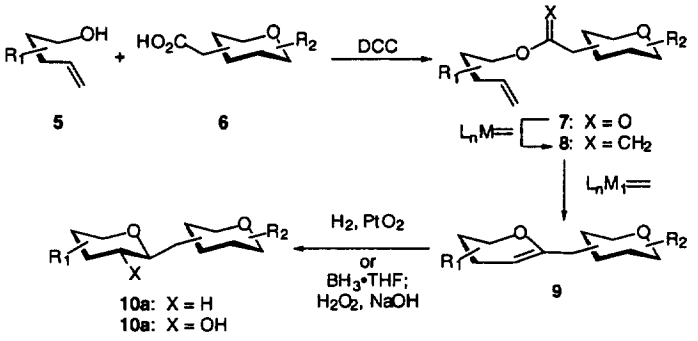
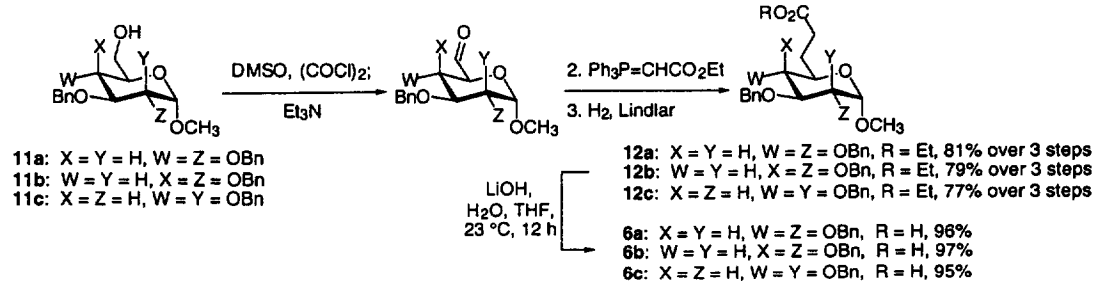
letter, we wish to present extension of our metathesis based methodology for preparation of carbon-linked disaccharides, specifically 1,6-linked-*C*-disaccharides, in which the interglycosidic oxygen atom of the parent *O*-disaccharide has been replaced[9] by a methylene group.[10]

Our methodology appeared to be well suited for the preparation of *C*-disaccharides, since the coupling of an appropriate sugar based olefin-alcohol **5** with sugar acid **6** should give ester **7**, (Scheme 1). Ring closing metathesis, either via a one- or two-pot method, was expected to give the requisite *C*-disaccharide glycal **9**, and subsequent functionalization (**9** → **10**) would deliver the desired *C*-disaccharides (**10a** or **10b**).



Scheme 1.

Olefin-alcohol coupling partner **5a** has been prepared previously,[11] and the preparation of the chain extended C-6 acids is straightforward as shown in Scheme 2.[12] This acid preparation is based on literature precedent from Kishi's maitotoxin work.[13] Acid **6d**[12] (Table 1) was prepared from the known α-allyl 2,3,4-tri-*O*-benzyl-D-*C*-mannoside by hydroboration (9-BBN; NaOH, H_2O_2, 89%), Swern oxidation, ($(COCl)_2$, DMSO, Et_3N) followed by chlorite oxidation of the resultant crude aldehyde ($NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O, 87% over 2 steps).

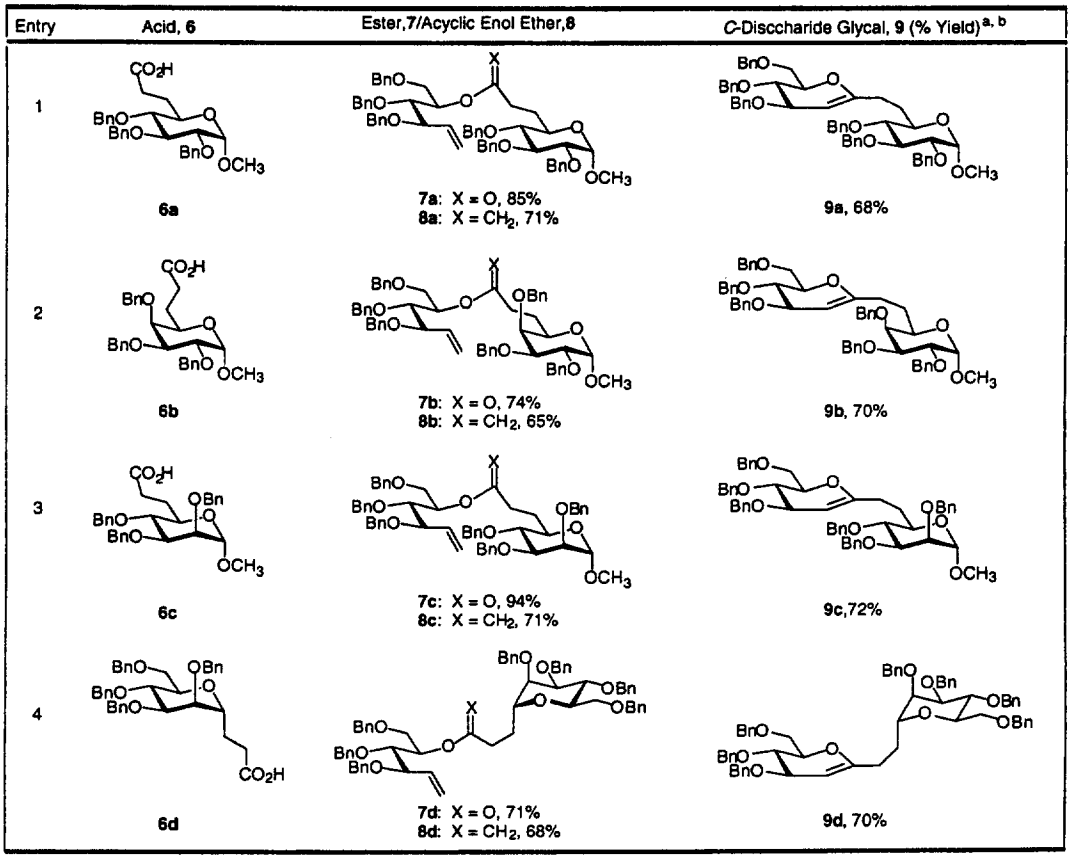


Scheme 2.

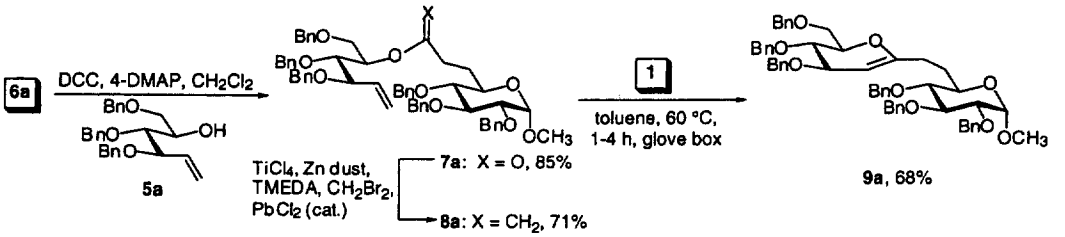
The synthetic sequence is illustrated in Scheme 3 with *gluco* acid **6a** (Table 1). DCC mediated coupling of the acids **6a–d** with **5a** (Scheme 3 and Table 1) proceeded in good yield to deliver esters **7a–d**, the remainder of the mass balance being recovered starting material.[12] Purification of the formed esters proved tedious and it proved to be more convenient to oxidize ($(COCl)_2$, DMSO, Et_3N, –78°C) unreacted alcohol **5a** to give the corresponding ketone in order to facilitate purification by silica gel chromatography.

The preparations of the acyclic enol ethers **8a–d** were carried out using the modified Takai procedure.[14] We were able to purify these rather unstable enol ethers via careful flash chromatography in the presence of 1–2% triethylamine. Exposure of the resultant acyclic enol ethers **8a–d** to the Schrock catalyst **1**,[1] under the prescribed conditions,[15] gave the desired *C*-disaccharide glycals **9a–d**[16] in good yield.[12] The

Table 1
Preparation of *C*-1 glycal disaccharides from sugar based olefin esters



a. Yields refer to chromatographically homogeneous (^{1}H NMR, 500 MHz) material. b. Reaction was carried out on 20-60 mg scale at 0.01-0.02 M in substrate using 10-25 mol % of 1.

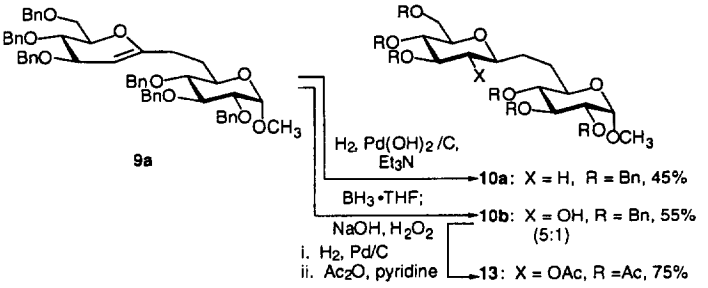


Scheme 3.

examples (**9a–d**) presented in Table 1 are among the most oxygenated substrates prepared with the Schrock catalyst reported to date. The yields for these reactions were quite good considering the dense substrate oxygenation and the presence of the allylic benzyloxy substituent that could potentially undergo elimination during alkylidene formation.

To demonstrate the utility of the chemistry described herein, we converted **9a** into the corresponding 2-deoxy-*gluco*-*C*-disaccharide **10a** and 2-*gluco*-*C*-disaccharide **10b** by standard methods (Scheme 4).[12,17] Selective reduction of the enol ether double bond in **9a** gave the protected 2-deoxy-*gluco*-*C*-disaccharide **10a**,[18] while hydroboration[19] gave the *gluco* isomer **10b** as the major compound (5:1, ^{1}H NMR, 500

MHz). Hydrogenolysis of the benzyl groups in **10b** was followed by acetylation to give the peracetylated *C*-disaccharide **13**. Work aimed at the preparation of higher congeners of this class of compounds is underway and will be reported in due course.



Scheme 4.

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16. Spectral data for **9a**: white solid: mp=100–101°C; $[\alpha]_D$=+23.3 (c=0.82, CH_2Cl_2); FT-IR (neat) 3087, 3062, 3030, 2920, 2864, 1673, 1496, 1453, 1359, 1328, 1291, 1207, 1178, 1158, 1138, 1094, 1072, 1028, 912, 735, 697 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.31–7.22 (m, 10H, Ph), 7.16–7.02 (m, 20H, Ph), 4.99 (d, 1H, *J*=11.1 Hz, OC*H*$_2$Ph), 4.89 (d, 1H, *J*=11.3 Hz, OC*H*$_2$Ph), 4.77–4.74 (m, 3H, *H*-2, OC*H*$_2$Ph), 4.59 (d, 1H, *J*=3.8 Hz, *H*-1′), 4.58 (d, 1H, *J*=11.2 Hz, OC*H*$_2$Ph), 4.55 (d, 1H, *J*=11.4 Hz, OC*H*$_2$Ph), 4.51 (d, 1H, *J*=11.9 Hz, OC*H*$_2$Ph), 4.46 (d, 1H, *J*=11.9 Hz, OC*H*$_2$Ph), 4.45 (d, 1H, *J*=12.1 Hz, OC*H*$_2$Ph), 4.39 (d, 1H, *J*=11.4 Hz, OC*H*$_2$Ph), 4.36 (d, 1H, *J*=11.1 Hz, OC*H*$_2$Ph), 4.32 (d, 1H, *J*=12.1 Hz, OC*H*$_2$Ph), 4.21–4.19 (m, 2H, *H*-3, 3′), 417–4.14 (m, 1H, *H*-5), 4.01 (dd, 1H, *J*=8.1, 5.8 Hz, *H*-4), 3.82–3.78 (m, 2H, *H*-6), 3.75 (dd, 1H, *J*=10.4, 3.1 Hz, *H*-5′), 3.50 (dd, 1H, *J*=9.6, 3.6 Hz, *H*-2′), 3.21 (t, 1H, *J*=9.4 Hz, *H*-4′), 3.13 (s, 3H, CH_3), 2.48–2.43 (m, 1H, *H*-7′), 2.28–2.23 (m, 2H, *H*-7′,6′), 1.75–1.69 (m, 1H, *H*-6′); ^{13}C NMR (125 MHz, C_6D_6) δ 156.4, 140.1, 139.8, 139.6, 139.6, 139.3, 128.8, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 98.4, 96.0, 82.7, 82.7, 81.6, 77.7, 77.0, 75.8, 75.5, 75.3, 73.8, 73.8, 73.1, 70.6, 70.1, 69.5, 55.3, 30.4, 29.8; HRMS (FAB): calcd for $C_{56}H_{60}O_9Na$ $(M+Na)^+$ 899.4135, found 899.4119.
17. The yields shown in Scheme 4 are not optimized.
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